ORAL GABAPENTIN FOR POSTOPERATIVE ANALGESIA IN THYROID SURGERY

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CERTIFICATE

This is to certify that the dissertation titled, 'oral Gabapentin for postoperative analgesia in thyroid surgery', submitted by Dr.Ajeeth.N.B , in partial fulfillment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamilnadu Dr.M.G.R. Medical University, Chennai is a bonafide record of the work done by him in the Department of Anaesthesiology, Madras Medical College, during the academic year 2005 – 2008.

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INTRODUCTION

The International Association of Study of Pain defines Pain as ‘ an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage ’

Patients often perceive postoperative pain as the most ominous part of undergoing a surgical procedure. In the past treatment of postoperative pain was given low priority by care givers and pain was considered a requisite part of the comprehensive postoperative experience

But with the improvement in the knowledge of the epidemiology and pathophysiology of pain, more attention has now been focused on the management of post-operative pain in an effort to improve quality of care and patient outcome.

Post thyroidectomy pain is attributed to the cervicotomy, intraoperative extension of neck, larygeal irritation caused by endo-tracheal tube and pain due to wound drains. This pain is usually treated with opioids and NSAIDS. But opioids are associated with many side effects like nausea and vomiting. Multimodal analgesic methods have come into vogue to reduce the side effects and to improve post-operative analgesia .

Also as evidence continues to accumulate concerning the role of central sensitization in postoperative pain, many

researchers have focused on methods to prevent central neuroplastic changes from occurring through the utilization of preemptive analgesic techniques. Effective preventative analgesic techniques may not only be useful in reducing acute pain but also chronic post-surgical pain and disability.Pre-emptive analgesic techniques described for thyroidectomies are wound infiltration with local anaesthetics, bilateral superficial plexus blocks, cervical epidural , pre-emptive administration of NSAIDS, anticonvulsants like Gabapentin and Pregabalin [1, 2].

Anticonvulsants are widely used to treat the allodynia and hyperalgesia associated with neuropathic pain. But they were not thought to be useful in inflammatory or post-operative pain. However accumulating laboratory and clinical evidence, including post operative analgesic trials suggests that gabapentin and its analogues such as Pregabalin are analgesics across a wide spectrum of pain states. This could be attributed to certain neural changes, common both to neuropathic and post tissue injury pain.

Recent studies have explored Gabapentin's role in post-operative pain relief. The objective of the present study was to examine the post-operative analgesic effectiveness, opioid sparing effect and side effects of pre-emptive Gabapentin in patients undergoing thyroid surgeries.

AIM

The aim of the present study was to examine the analgesic effectiveness, opioid-sparing effects and side effects associated with pre-emptive administration of gabapentin in patients undergoing thyroid surgeries.

REVIEW OF LITERATURE

1) Mark J. Field, Elizabeth F. Holloman et al studied the effect of Gabapentin and *S*-(+)-3-Isobutylgaba in a Rat Model of Postoperative Pain. An incision of the plantaris muscle of a hind paw induced thermal hyperalgesia and tactile allodynia lasting at least 3 days. Postoperative testing was carried out using the plantar test for thermal hyperalgesia and von Frey hairs for tactile allodynia. A single s.c. dose of gabapentin, 1 h before surgery, dose-dependently (3-30 mg/kg) blocked the development of allodynia and hyperalgesia with a minimum effective dose (MED) of 10 and 30 mg/kg, respectively. The highest dose of gabapentin prevented development of hyperalgesia and allodynia for 24 and 49 h, respectively.

2) Werner MU, Perkins FM et al studied the effect of gabapentin in acute inflammatory pain in humans. Twenty-two volunteers were investigated in a double-blind, randomized, placebo-controlled cross-over study. Gabapentin 1,200 mg or placebo was given on 2 separate study days. Three hours after drug administration, a first-degree burn injury was produced on the medial aspect of the nondominant calf . Gabapentin diminished the decrease in mechanical pain threshold in the burn area and

reduced secondary hyperalgesia. Ratings of drowsiness and unsteadiness during walking were significantly higher for gabapentin than for placebo. The study indicates that gabapentin has no analgesic effect in normal skin, but may reduce primary mechanical allodynia in acute inflammation following a thermal injury. These observations suggest a clinical potential of gabapentin in the treatment of postoperative pain.

3) Dirks J. Peterson KL et al tried to link data from animal models and clinical trials for chronic pain by investigating the effect of gabapentin on acute nociception and experimentally induced cutaneous hyperalgesia in healthy volunteers. study showed oral gabapentin profoundly suppressed established cutaneous sensitization on the forearm and prevented development of cutaneous sensitization on the thigh. Thermal nociception in normal skin was unchanged.

Many randomized clinical studies explored the role of gabapentin in reducing peri-operative pain .

4) Turan b,Kumaralingalou et al Investigated the effects of gabapentin on acute postoperative pain and morphine consumption in patients undergoing spinal surgery. Their study showed that preoperative oral gabapentin decreased pain scores in the early postoperative period and

postoperative morphine consumption in spinal surgery patients while decreasing some morphine-associated side effects.

5) Dilek Memiş, MD*, Pinar Usar, et al investigated, in a randomized, placebo-controlled, double-blind study, the efficacy and safety of gabapentin on pain after abdominal hysterectomy and on tramadol consumption in patients.The VAS scores in the sitting and supine position at 1, 4, 8, 12, 16, and 20 hour were significantly lower in the gabapentin group when compared with the placebo group up to 20 h after surgery. The tramadol consumption at 12, 16, 20, and 24 h and total tramadol consumption were significantly less in the gabapentin group when compared with placebo group. Sedation scores were similar at all the measured times. There were no differences between groups in adverse effects.

6) Turan A, Memis D,[24] investigated the efficacy and safety of gabapentin in patients who underwent rhinoplasty or endoscopic sinus surgery patients under monitored anesthesia care. . Postoperative pain scores and intraoperative pain scores at 45 and 60 min were significantly lower in the gabapentin group. Fentanyl (122 ± 40 μg versus 148 ± 42 μg; $P < 0.05$) and diclofenac (33 ± 53 mg versus 111 ± 92 mg; $P < 0.001$) consumption was smaller and the time to first analgesic request (18 ± 9 h versus 9 ± 7 h; $P < 0.001$) was longer in the gabapentin group. A more

frequent incidence of dizziness was found in the gabapentin (versus placebo) group (24% versus 4%, respectively).

7) Dirks J, Fredensborg BB et al studied the effect of a single dose of 1,200 mg oral gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy result showed a substantial reduction in postoperative morphine consumption and movement-related pain after radical mastectomy, without significant side effects.

8) Chandra Kant Pandey, MD, Shio Priye,et al Four hundred fifty-nine ASA I and II patients were randomly assigned to receive 300 mg gabapentin, 100 mg tramadol or placebo in a double-blind manner two hours before laparoscopic cholecystectomy under general anesthesia.they found out that Significantly less fentanyl was consumed in the gabapentin group than in the tramadol and placebo groups. Sedation , nausea/retching/vomiting were the commonest side effects in the gabapentin group whereas respiratory depression was the commonest in the tramadol group and vertigoin the placebo group

9) Rorarius MG,Mennander S et al gave 1200 mg of gabapentin or 15 mg of oxazepam (active placebo) 2.5 h prior to induction of anaesthesia to patients undergoing elective vaginal hysterectomy in an active placebo-controlled, double blind, randomised study. they found that Gabapentin

reduced the need for additional postoperative pain treatment by 40% during the first 20 postoperative hours. During the first 2 postoperative hours pain scores at rest and worst pain score (VAS 0-100 mm) were significantly higher in the active placebo group compared to the gabapentin-treated patients. Additionally, pretreatment with gabapentin reduced the degree of postoperative nausea and incidence of vomiting.

10) Al-Mujadi H, A-Refai AR [19] et al gave gabapentin 1200 mg or placebo two hours prior to induction of anesthesia to patients undergoing elective thyroidectomy. They found that overall, pain scores at rest and during swallowing in the gabapentin group were significantly lower when compared with the placebo group. No significant differences in side effects were observed between groups.

11) Pandey CK, Navkar DV,et al evaluated the optimal preemptive dose of gabapentin for postoperative pain relief after single-level lumbar diskectomy and its effect on fentanyl consumption during the initial 24 hours. Patients were divided into five groups to receive placebo or gabapentin 300, 600, 900, or 1200 mg 2 hours before surgery.).they found that Patients who received gabapentin 600, 900, and 1200 mg had lower VAS scores at all time points than patients who received gabapentin 300 mg ($P < 0.05$). Increasing the dose of gabapentin from 600 to 1200 mg did not decrease the VAS score, nor did the increasing

dose of gabapentin significantly decrease fentanyl consumption. Thus, gabapentin 600 mg is the optimal dose for postoperative pain relief.

12)Klaus Eckhardt, MD, Susanne Ammon, MD, et al investigated, in a randomized, placebo-controlled, double-blinded study, the pharmacodynamic and pharmacokinetic interaction of GBP and morphine in 12 healthy male volunteers. Morphine (60 mg, controlled release) or placebo was administered at 8:00 AM, and GBP (600 mg) or placebo was administered at 10:00 AM, thus comparing the analgesic effect of placebo + GBP (600 mg) with placebo + placebo and morphine (60 mg) + GBP in comparison to morphine plus placebo by using the cold pressor test.The results showed that gabapentin enhanced the acute analgesic effect of morphine. Furthermore, the plasma concentration of gabapentin was increased when morphine was administered concomitantly.

There were some metanalysis and review articles which analyzed the various studies of gabapentin as a pre emptive analgesic.

13) Seib RK,Paul JE et al Conducted a metaanalysis to find out whether gabapentin reduces pain scores, analgesia consumption, and/or analgesia-related side effects in the first 24 hr following surgery. they conclude that Although gabapentin given preoperatively decreases pain scores and

analgesic consumption in the first 24 hr after surgery, the clinical significance of this finding has yet to be determined.

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14) Ho KY, Gan TJ, Habib AS. Did a systematic review of randomized controlled trials. When gabapentin was administered at doses less than 1200 mg, pain intensity was also lower at 6 h (WMD, -22.43 mm) and 24 h (WMD, -13.18 mm). Cumulative 24 h opioid consumption was also lower (WMD, -7.25 mg). Gabapentin was associated with an increased risk of sedation (Peto OR 3.86; 95% CI 2.50-5.94) but less opioid-related side effects such as vomiting (Peto OR 0.58; 95% CI 0.39-0.86) and pruritus (Peto OR 0.27; 95% CI 0.10-0.74). In conclusion, gabapentin has an analgesic and opioid-sparing effect in acute postoperative pain management when used in conjunction with opioids.

METHODS: Sixty patients scheduled for abdominal hysterectomy were randomized to receive orally gabapentin 400 mg 6 hourly or placebo. Treatment started 18 h preoperatively and continued for 5 postoperative days. Pain (visual analogue score) and consumption of morphine for 48 h and of oral paracetamol/codeine were recorded after 2, 4, 8, 24 and 48 h and on days 3-5 postoperatively. After 1 month, patients were

interviewed by phone for pain, and analgesic intake after hospital discharge

15)Mathiesen O, Møiniche S, Dahl JB.did a qualitative and quantitative systematic review, with focus on procedure of Gabapentin and postoperative pain: Twenty-three trials with 1529 patients were included. In 12 of 16 studies with data on postoperative opioid requirement, the reported 24-hour opioid consumption was significantly reduced with gabapentin. Quantitative analysis of five trials in abdominal hysterectomy showed a significant reduction in morphine consumption (WMD - 13 mg, 95% confidence interval (CI) -19 to -8 mg), and in early pain scores at rest (WMD - 11 mm on the VAS, 95% CI -12 to -2 mm) and during activity (WMD -8 mm on the VAS; 95% CI -13 to -3 mm), favouring gabapentin. In spinal surgery, (4 trials), analyses demonstrated a significant reduction in morphine consumption (WMD of - 31 mg (95%CI - 53 to -10 mg) and pain scores, early (WMD - 17 mm on the VAS; 95 % CI -31 to -3 mm) and late (WMD -12 mm on the VAS; 95% CI -23 to -1 mm) also favouring gabapentin treatment. Nausea was reduced with gabapentin in abdominal hysterectomy (RR 0.7; 95 % CI 0.5 to 0.9). Other side-effects were unaffected

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16)Tiippana EM, Hamunen K, Kontinen VK, also E.did a A systematic review of efficacy and safety to find if surgical patients benefit from perioperative gabapentin/pregabalin. They found that Pain relief was better in the gabapentin groups compared with the control groups. The opioid-sparing effect during the first 24 h after a single dose of gabapentin 300-1200 mg, administered 1-2 h preoperatively, ranged from 20% to 62%. The combined effect of a single dose of gabapentin was a reduction of opioid consumption equivalent to 30 +/- 4 mg of morphine (mean +/- 95% CI) during the first 24 h after surgery. Metaregression analysis suggested that the gabapentin-induced reduction in the 24-h opioid consumption was not significantly dependent on the gabapentin dose. Gabapentin reduced opioid-related adverse effects, such as nausea, vomiting, and urinary retention (number-needed-to-treat 25, 6, and 7, respectively). The most common adverse effects of the gabapentinoids were sedation and dizziness (number-needed-to-harm 35 and 12, respectively

17)Gilron I. Can J Anaesth. 2006 Jun;53(6):562-71reviewed preclinical evidence and clinical trial data describing the efficacy and safety of anticonvulsant drugs in the setting of postoperative pain management. He suggested that anticonvulsant drugs may alleviate postoperative anxiety,

accelerate postoperative functional recovery and reduce chronic postsurgical pain.

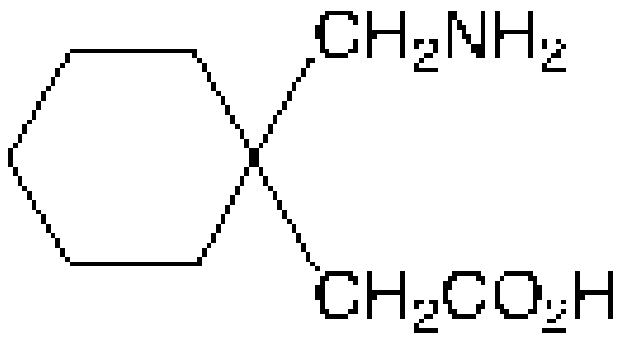
18) **Wiffen PJ**, **McQuay HJ** et al.did a Cochrane data review to evaluate the analgesic effectiveness and adverse effects of gabapentin for pain management in clinical practice. SEARCH STRATEGY: Randomised trials of gabapentin in acute, chronic or cancer pain were identified by MEDLINE (1966-Nov 2004), Data were extracted by two independent reviewers, and trials were quality scored. Numbers-needed-to-treat (NNTs) were calculated, where possible, from dichotomous data for effectiveness, adverse effects and drug-related study withdrawal. Fourteen reports describing 15 studies of gabapentin were considered eligible (1468 participants)The study in acute post-operative pain (70 participants) showed no benefit for gabapentin compared to placebo for pain at rest.In chronic pain, the NNT for improvement in all trials with evaluable data is 4.3 (95%CI 3.5-5.7). Forty two percent of participants improved on gabapentin compared to 19% on placebo. The number needed to harm(NNH) for adverse events leading to withdrawal from a trial was not significant. Fourteen percent of participants withdrew from active arms compared to 10% in placebo arms. The NNH for minor harm was 3.7 (95% CI 2.4 to 5.4). The NNT for effective pain relief in diabetic neuropathy was 2.9 (95% CI 2.2 to 4.3) and for post herpetic neuralgia

3.9 (95% CI 3 to 5.7). They concluded that there is evidence to show that gabapentin is effective in neuropathic pain. There is limited evidence to show that gabapentin is ineffective in acute pain.

PHARMACOLOGY OF GABAPENTIN

Gabapentin was introduced for the treatment of epilepsy in the early 1990s. Several years later, anecdotal reports describing the efficacy of gabapentin for the treatment of neuropathic pain began to appear and off-label prescribing for this indication became widespread. Large placebo-controlled, double-blind trials confirmed these reports and gabapentin became licensed in many countries for the treatment of neuropathic pain.

STRUCTURE OF GABAPENTIN



Gabapentin is described as 1-(aminomethyl)cyclohexaneacetic acid with a molecular formula of C9H17NO2 and a molecular weight of 171.24. The structural formula of gabapentin is:

Gabapentin is a white to off-white crystalline solid with a pKa1 of 3.7 and a pKa2 of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is –1.25

Pharmacokinetics and Drug Metabolism

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

Oral Bioavailability:

Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 50% following 600mg oral. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and Cmax).

Distribution:

Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58±6 L (Mean ±SD).

Elimination:

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Age: Oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those under 30 years of age to about 125 mL/min in those over 70 years of age. Renal clearance (CLr) also declined with age, which can largely be explained by the age related decline in renal function.

Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women,it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

ANALGESIC EFFECT OF GABAPENTIN

Despite intensive study, the basis of gabapentin analgesia remains uncertain. But in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful

stimuli). In particular, gabapentin prevents pain-related responses in several models of neuropathic pain in rats or mice (e.g. spinal nerve ligation models, streptozocin-induced diabetes model, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test). Gabapentin did not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase, acetic acid abdominal constriction test, footpad heat irradiation test). The relevance of these models to human pain is not known.

Gabapentin was developed as an analogue to the neurotransmitter GABA but has since been shown not to interact with either GABAa or GABAb receptors. GABA-ergic function could be potentiated without direct interaction with GABA receptors by increasing the concentration of GABA in neuronal tissue through release of GABA from nerve terminals,enzyme effects, or decreased GABA breakdown.Another possible mechanism is mobilization of intracellular GABA via gabapentin sensitive transporters.

However the best evidence comes from studies of gabapentin on a specific gabapentin - binding protein found in brain and spinal cord. The binding site a2d ,is a subunit of n-type voltage - gated calcium channel found in high density in cerebral cortex, superficial dorsal horn, cerebellum and hippocampus studies in spinal

cord dorsal horn have found that gabapentin binding is primarily post-synaptic.GABA itself has no activity at this binding site, but gabapentin analogues that bind to a2d subunit do appear to have analgesic activity

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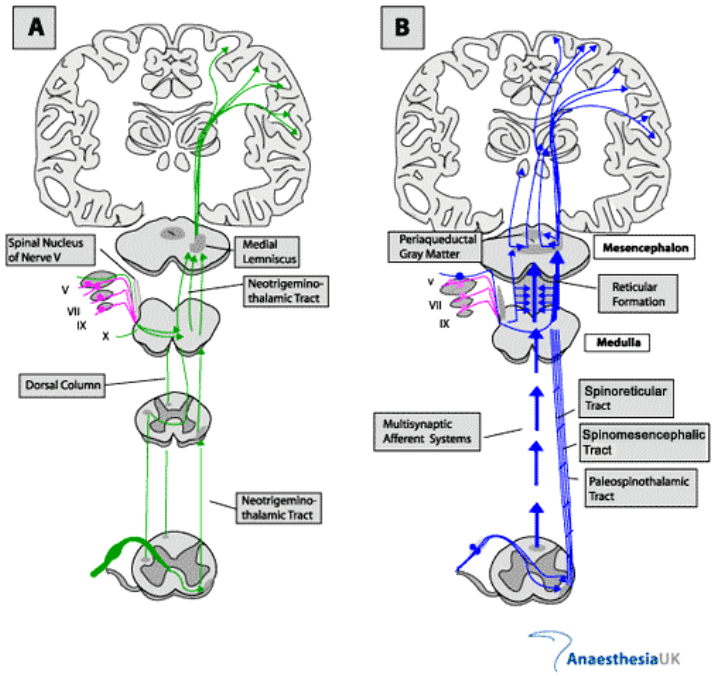
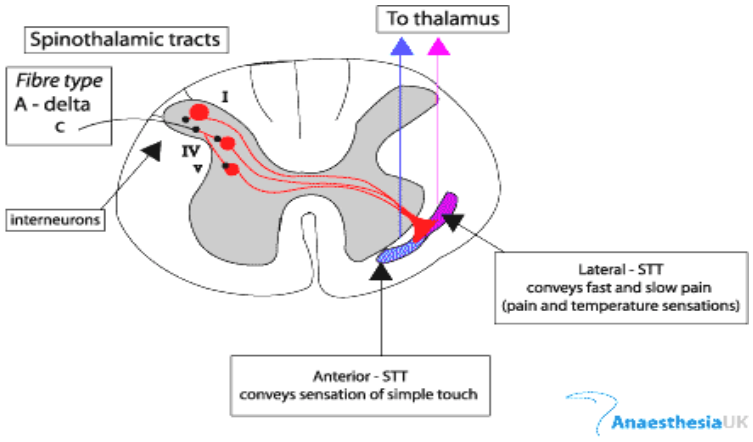


SPINOTHALAMIC TRACT



Arrangement of pain pathways in spinal cord

NEUROANATOMY OF PAIN

Traditionally there have been two major theories of pain sensation. Specificity theory, postulated by Von frey proposes that pain as well as other modalities like touch, warmth and cold each has a distinctive end organ in the skin and that each 'stimulus specific' end organ is connected by its own pathway to the brain. A second theory of which Gold Schneider was an early protagonist held that any sensory stimulus if sufficiently intense could produce pain. According to this there are no distinct pain receptors and the sensation of pain is the result of the summation of impulses excited by thermal stimuli or pressure applied to the skin. Originally called the intensive theory it later came to be known as the Pattern or Summation theory. More recent investigations have reconciled to these opposing views.

It is now well established that two types of afferent fibers, the distal axons of primary afferent neurons, respond maximally to noxious stimuli. One type is, the very fine, unmyelinated, so called c fiber (0.4-1.1μm in diameter) and the other is the thinly myelinated A delta

fiber (1.0-5.0μm in diameter). They terminate peripherally at the free nerve endings in the skin and other organs. These free nerve endings are fine, profusely branched nerve fibers that are covered by Schwann cells and contain little or no 'myelin' fibers, respond most effectively to noxious stimuli.

PAIN PATHWAYS

Primary afferent neurons are located in the dorsal root ganglia, which lie in the vertebral foramina at each spinal cord level. Pain fibers may ascend or descend one or three spinal segments in Lissauer's tract before synapsing with second order neurons in the gray matter of the ipsilateral dorsal horn. Central extensions of these nerve cells project via the dorsal root ganglia to the dorsal horn of the spinal cord. Spinal cord grey matter was divided into 10 lamina by Rexed. The first 6 lamina, which make up the dorsal horn receive all the afferent neural, and represent the principal site of modulation of pain by ascending and descending pathways. Most nociceptive C fibers send collaterals to, or terminate on, second order neurons in lamina I , II or V. Nociceptive Ad fibers terminate in I,V or X. lamina II is also called Substantia Gelatinosa, contains many interneurons and plays a major role in modulation of pain. It is also the major site of action of opioids. Lamina III and IV receive non-nociceptive sensory input. Cell bodies of pre-

ganglionic sympathetic fibers are in lamina VII. Lamina VIII and IX make up the anterior motor horn.

Spinothalamic tract

The Spinothalamic tract(STT) transmits information about temperature and pain, as well as “simple” touch (i.e. related to localisation of stimulus) and visceral sensations. It mediates the discriminative and arousal-emotional components of these sensations by separating out the “fast” (discriminative aspect) and “slow” (affective aspect) components of pain into different regions of the tract that are transmitted in parallel to the thalamus. Discriminative pain reaches the thalamus directly without making connections elsewhere in the nervous system, whereas arousal-emotional pain reaches the thalamus indirectly via connections with brainstem regions. Slow pain is also transmitted by other pathways such as the spinoreticular tract. The STT may be divided into the lateral STT and the anterior STT. Pain and temperature is transmitted mainly in the lateral STT. The lateral-STT transmits the sensations of both fast and slow pain. The anterior STT conveys sensations of simple touch (stimulus localisation). The STT ascends the entire length of the cord and the brainstem, staying in about the same location all the way up. It is here in the brainstem that the

different modalities separate out to terminate in different thalamic and brainstem nuclei. The fast pain STT axons terminate in the ventroposterior nucleus, which comprises the ventral posterolateral (VPL) and ventral posteromedial (VPM) and the posterior (PO) nuclei. These axons seem to mediate mainly the sense of “simple touch” and pain. These sensations are separated within the thalamus: neurons in the VPL and VPM do not respond specifically to noxious stimulation, whereas cells in the PO receive inputs from both low- and high-threshold afferents. These cells are associated with the conscious perception of pain.

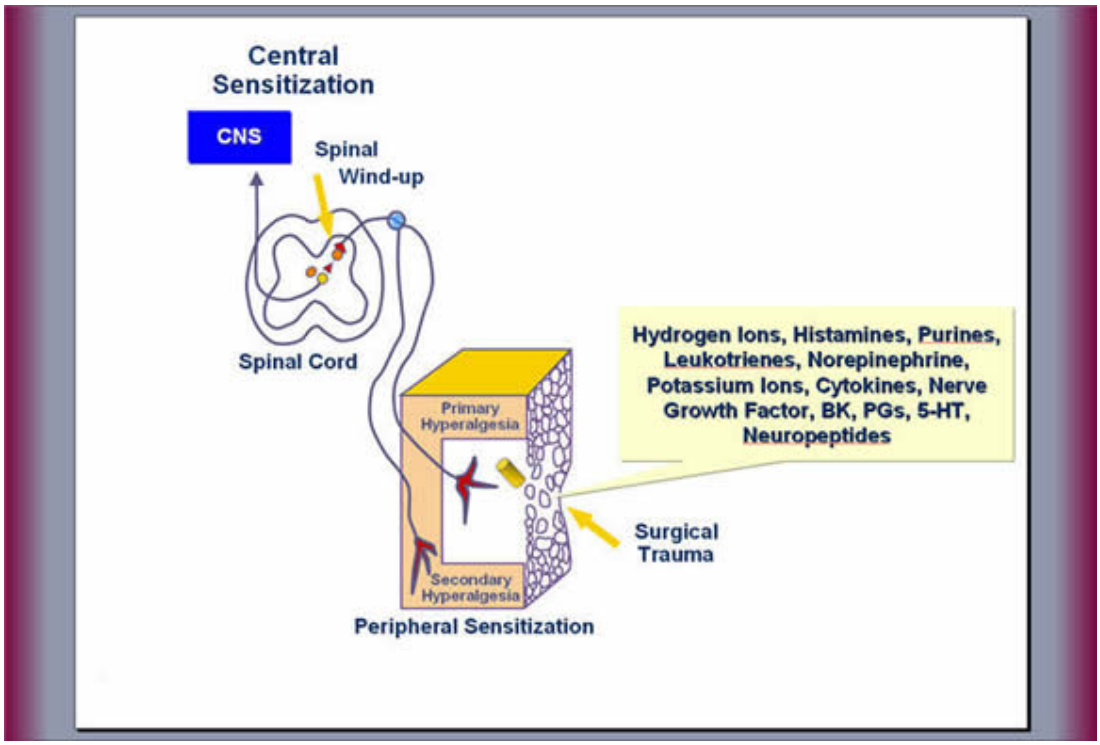
The slow pain-STT axons innervate the non-specific intralaminar nuclei of the thalamus, and the reticular formation in the brainstem. These axons form at least part of the forebrain pain pathway associated with the affective quality (unpleasantness and fear of further injury) of pain and can be dissociated from the discriminative quality (the type and nature of the injury itself). The projections to the reticular formation may underlie the arousal effects of painful stimuli. The arousal itself may activate noradrenergic neurons in the locus coeruleus, and thus decrease the upward pain transmission.This may be an example of a negative feedback loop in the nervous system.

Comparison of central pathways for pain transmission

	Direct (fast)	**Indirect (slow)**
Tract	Lateral-STT	Lateral-STT
Origin	Lamina I & IV, V	Lamina I, IV,V,
Somatotopic	Yes	No
Body representation	Contralateral	Bilateral
Synapse in reticular	No	Yes
Sub-cortical targets	None	Hypothalamus
Thalamic nucleus	Ventral posterolateral	Intra-laminar nuclei
Cortical location	Parietal lobe (SI	Cingulate gyrus
Role	Discriminative pain	Affective-arousal
Other functions	Temperature	

It has long been known that the STT is an important pain pathway because when it is damaged, pain and temperature sense is abolished on the contralateral side of the body below the lesion. It has been used, as a last resort, by surgeons to relieve intractable cancer pain. However, pain is not permanently abolished because of preservation of one side of the bilateral indirect pathways. Also, the transmission of simple tactile modalities (detection, location) via the anterior STT explains why touch sensation is preserved in people with dorsal column lesions (although they are unable to discriminate the nature of the stimulus.

PHYSIOLOGY OF PAIN



PHYSIOLOGY OF PAIN

Surgical trauma leads to the release of inflammatory mediators at the site of injury, resulting in a reduction in the pain threshold at the site of injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia). Peripheral sensitization results from a reduction in the threshold of nociceptor afferent terminals secondary to surgical trauma. Central sensitization is an activity-dependent increase in the excitability of spinal neurons (**spinal**

wind-up) as a result of persistent exposure to afferent input from peripheral neurons.

Operative procedures produce an initial delivery of nociceptive signals and generate a secondary inflammatory response, both of which contribute substantially to postoperative pain. The signals have the capacity to initiate prolonged changes in both the peripheral and central nervous system that will lead to the amplification and prolongation of postoperative pain. Increased peripheral sensitization to pain (a reduction in the threshold of nociceptor afferent peripheral terminals) is a result of inflammation at the site of surgical trauma

Central sensitization, an activity-dependent increase in the excitability of spinal neurons, is a result of persistent exposure to nociceptive afferent input from the peripheral neurons in the skin. Taken together (incoming pain signals and inflammation), these two processes contribute to the postoperative hypersensitivity state ("spinal windup") that is responsible for a decrease in the pain threshold, both at the site of injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia) . This is the mechanism by which pain may be prolonged beyond the duration normally expected with an acute insult. Prolonged central sensitization has the capacity to lead to permanent alterations in the CNS including the death of inhibitory neurons,

replacement with new afferent excitatory neurons, and the establishment of aberrant excitatory synaptic connections. These alterations result in a prolonged state of sensitization resulting in intractable post-surgical pain that is unresponsive to many analgesics.

PRE-EMPTIVE ANALGESIA

As evidence continues to accumulate concerning the role of sensitization in the prolongation of postoperative pain, many researchers have focused on methods which not only treat the symptoms as they occur, but prevent windup from occurring through the utilization of preemptive analgesic techniques. The evidence in support of preemptive analgesia has been equivocal with one recent systematic review of the literature demonstrating no beneficial effect while a more recent review demonstrating an overall benefit of this concept. However, the concept of preemptive analgesia has evolved beyond the importance of only reducing the nociceptive afferent input brought about by the surgical incision. The term preventative analgesia was introduced to emphasize the fact that central neuroplasticity is induced by both pre-, intra-, and postoperative nociceptive inputs. Thus the goal of preventative analgesia is to reduce central sensitization that comes from noxious inputs arising throughout the entire perioperative period and not just from those occurring during the surgical incision.

Preemptive treatment should be directed at the periphery, along the sensory axons, and central neurons. This can be accomplished with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, local anesthetics, alpha -2 agonists (clonidine), anticonvulsants (gabapentin and pregabalin), cryotherapy, and opioids, either alone or in combination

PAIN ASSESSMENT METHODS

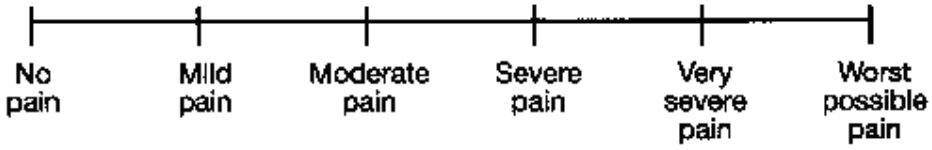
In verbal patients, self-report is the gold standard, and external signs of pain or distress (eg, crying, wincing, rocking) are secondary. For patients who have difficulty communicating and for young children, nonverbal indicators (behavioral and sometimes physiologic) may need to be the primary source of information. Formal measures include verbal category scales (eg, mild, moderate, severe), numeric scales, and the Visual Analog Scale (VAS). For the numeric scale, patients are asked to rate their pain from 0 to 10 (0 = no pain; 10 = “the worst pain ever”). For the VAS, patients make a hash mark representing their degree of pain on an unmarked 10-cm line with the left side labeled “no pain” and the right side labeled “unbearable pain.” The pain score is distance in mm from the left end of the line. Children and patients with limited literacy or known developmental

problems may select from images of faces ranging from smiling to contorted with pain or from fruits of varying sizes to convey their perception of pain severity.

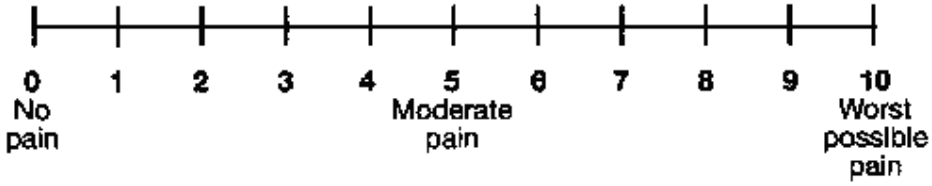
VISUAL ANALOGUE SCALE

Visual analogue scale provides a simple, efficient and noninvasive measure of the intensity of pain. It is a 10 cm long scale with the two end points labeled ‘no pain’ and ‘worst possible pain’. The patient makes a mark on the scale at a point corresponding to the intensity of pain he or she presently feels. The distance in cm from the lower end of the scale to the mark is the numerical value of pain score.

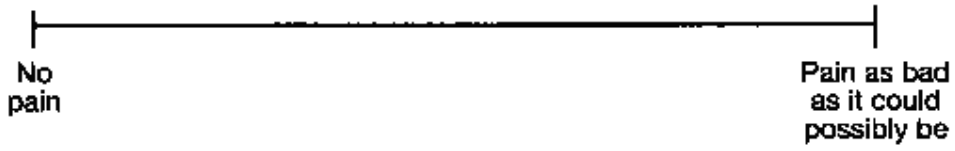
Simple Descriptive Pain Intensity Scale[1]



0–10 Numeric Pain Intensity Scale[1]



Visual Analog Scale (VAS)[2]



[1] If used as a graphic rating scale, a 10 cm baseline is recommended.
[2] A 10-cm baseline is recommended for VAS scales.

MATERIALS AND METHODS

This study was conducted in patients who underwent elective thyroid surgeries at Government General Hospital at Madras Medical College. The study was approved by institutional ethics committee and informed written consent was obtained from all the patients. The study was designed to be randomized, double blind and placebo controlled. Adults of either sex of American society of Anesthesiologists physical status –I or II scheduled for elective thyroid surgeries were eligible for the study. Excluded were patients of ASA physical status -III or IV ,with known allergy to gabapentin, chronic pain or recent intake of analgesics or corticosteroids, history of drug or alcohol abuse or impaired renal or liver function.All patients were instructed pre-operatively on the use of Visual Analogue Scale. Patients were randomly assigned to receive oral Gabapentin 600 mg or placebo capsule 2hours before surgery with the help of a computer generated table of random numbers.

All patients received oral Diazepam 10mg on the night before surgery. All of them were also premedicated with fentanyl 2 $\mu g\ kg^{-1}$ and Glycopyrrolate 0.2 mg. Anesthesia was induced with propofol 2mg/kg and succinylcholine 1.5mg/kg was given to aid tracheal intubation. General anesthesia was maintained with Isoflurane1% and

66% nitrous oxide in oxygen. Isoflurane was adjusted to maintain adequate depth of anesthesia. Mechanical ventilation was adjusted to maintain normocarbia .Neuromuscular blockade was maintained with Vecuronium. Fentanyl 1 μg kg^{-1} was repeated hourly and titrated to intensity of surgical stimulus. Continuous electro-cardiogram and heart rate, pulse oximetery, non invasive blood pressure and end tidal carbon dioxide were monitored during anesthesia. At the end of surgery residual neuromuscular blockade was reversed with Neostigmine 0.04mg/kg *iv* and Glycopyrrolate 0.4mg iv. After tracheal extubation patients were transferred to the post anesthesia care unit (PACU)

In PACU a resident doctor who was blinded with respect to the treatment group recorded the VAS pain scores at first hour following surgery, then at two ,six, 12 , 18 , and 24 hours in the post operative period. Fentanyl 1 μg kg^{-1} was given to the patient by the staff nurse as a rescue analgesic at the patients demand or if VAS score is 5 or greater. The total fentanyl consumption in 24 hours was recorded. Sedation was graded using Ramsay sedation score. Side effects including Nausea and vomiting, Respiratory depression, dizziness and diarrhea were recorded. Ondansetron 4 mg iv mg iv was used to treat nausea and vomiting. A Patient was considered to have respiratory depression if his respiratory rate <8 or oxygen saturation was less than 90 %.

RAMSAY SEDATION SCORE	
1	Anxious ,Agitated or Restless
2	Cooperative, Oriented and Tranquil
3	Responds to command
4	Asleep but has a brisk response to a light glabellar tap or loud auditory stimulus
5	Asleep but has a sluggish response to a light glabellar tap or loud auditory stimulus
6	Asleep, no response

OBSERVATION AND RESULTS

Eighty consecutive patients who fulfilled the inclusion criteria were enrolled in the study. Surgery was postponed for three patients in Placebo group and two patients in Gabapentin group. One patient in placebo group developed immediate postoperative stridor and another patient in gabapentin group had to undergo re-exploration for reactionary hemorrhage. Both were excluded from the study. Three patients from placebo group and two patients from gabapentin group were excluded because they received a different analgesic which was prescribed by surgeon. Thus data from 35 patients of gabapentin group and 33 patients of placebo group were included and analyzed.

After completion of study the data was unblinded and analyzed using statistical software package SPSS 10. Demographic data was analyzed with two sample student's t-test. Fentanyl consumption and VAS scores were analyzed using two way ANOVA with drug administered as one factor and the time interval as the second. This was statistically significant. Then unpaired t test was performed at each time period to ascertain the pattern and magnitude of difference. The incidence of adverse events was compared using Chi-square test. Data was reported as mean± standard deviation. A p- value of < 0.05 was considered statistically significant

There was no difference between the groups with respect to demographic characteristics or the type and duration of surgery.

DEMOGRAPHIC DATA			p-value
VARIABLE	GABAPENTIN(n=35)	PLACEBO(n=33)	
AGE(yr)	35.94 ± 10.52	39.69 ± 10.69	0.768[$]
MALE / FEMALE	7 / 28	6 / 27	0.467[$]
WEIGHT(kg)	52.86 ± 9.23	53.18 ± 7.27	0.71[$]

Average age was 35.94± 10.52 years in Gabapentin group and 39.69 ± 10.69 years in placebo group with a p value of 0.768. There was no statistically significant difference in the body weight between the two groups - 52.86 ± 9.23 kg in gabapentin group and 53.18 ± 7.27 kg in placebo group (p=0.71).

SURGICAL DATA		
DURATION OF SURGERY(min)	92.29 ± 38.8	88.78 ± 33.52
SURGICAL METHOD Hemithyroidectomy / Subtotal thyroidectomy / Total thyroidectomy	10 / 20 / 5	11 / 19 / 3

Duration of surgery was also similar in both groups - 92.29 ± 38.8 minutes in gabapentin group and 88.78 ± 33.52minutes in placebo group (p=0.118).The distribution of method of surgery was also similar in both groups.

Post-operative VAS Pain scores				
	Gabapentin(n=35)		***Placebo(n=33)***	
Hours	**At rest**	**Swallowing**	**At rest**	**Swallowing**
T1	3.6 ±1.9$	4.57 ±2.1$	4.24 ±2.2 $	5.3 ±2.2 $
T2	3.26 ±1.4*	4.26 ±1.6*	4.21 ±2.1*	4.9 ±2.3*
T6	3.31 ±1.5*	3.94 ±1.6*	4.63 ±1.5 *	5.5 ±1.7*
T12	2.74 ±1.7*	3.37 ±1.9*	4.09 ±1.3*	5.18 ±1.5*
T18	2.2 ±1.4*	2.65 ±1.5*	3.15 ±1.6*	4.12 ±1.8*
T24	1.69 ±1.4*	2.0 ±1.3*	2.3 ±1.2*	3.24 ±1.7*

$ not significant p value > 0.05

*statistically significant p value<0.05

The VAS scores at rest and swallowing were significantly lesser in Gabapentin group compared with the placebo group, except at the 1st hour.

At first hour even though the VAS score was higher in placebo group the difference was not statistically significant.

FENTANYL TOTAL DOSE		
	Total Dose	*p* value
Gabapentin	141.3 ±59.7	0.0125*
Placebo	198.9 ±54.4	

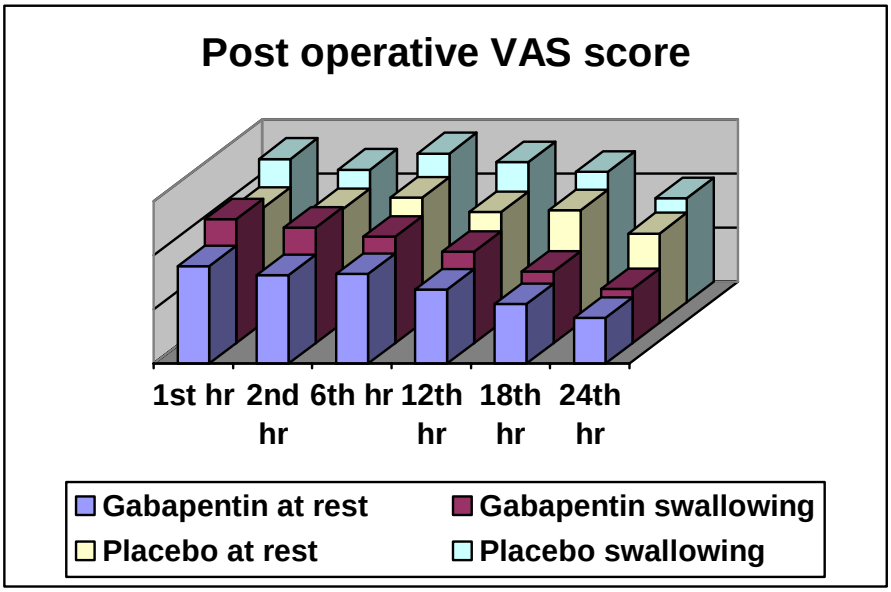
The total fentanyl consumption in Gabapentin group was 141.3mg which was significantly less than placebo group 198.9mg (p=0.0125).

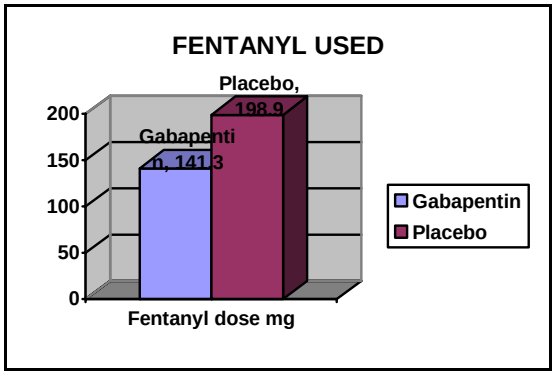
POST-OPERATIVE COMPLICATION								
	PONV	*p*	Vertigo	*p*	Respiratory Depression	*p*	Ramsay Sedation Score	*p*
Gabapentin	11 (31.43%)	0.08[$]	19 (54.28%)	0.013*	4 11.43%	0.257[$]	3.49±0.57	0.0125*
Placebo	18 (54.54%)		7 (21.21%)		2 6.06%		2.48±0.61	

18 patients (54.54%) in placebo group had post operative nausea or vomiting in comparison to 11 patients (31.43%) in gabapentin group which was not statistically significant (p=0.08). There was significant difference in the incidence of number of patients who had vertigo between gabapentin group 19 patients (54.28%) and placebo group 7 (21.21%) (p=0.013)

There was no difference in the incidence of respiratory depression in both groups. 4 patients11.43% of gabapentin group and 2 patients 6.06% of placebo group had respiratory depression (p=0.257)

The mean Ramsay Sedation Score was higher in Gabapentin group 3.49±0.57 compared to placebo group 2.48±0.61. The difference was statistically significant with a p value of 0.0125.


Post operative VAS score
1st hr
2nd hr
6th hr
12th hr
18th hr
24th hr
Gabapentin at rest
Gabapentin swallowing
Placebo at rest
Placebo swallowing


FENTANYL USED
Placebo, 198.9
Gabapenti n, 141.3
200
150
100
50
0
Gabapentin
Placebo
Fentanyl dose mg

DISCUSSION

The result of this study shows that pain scores at rest and swallowing are significantly less at all times in the first 24 hours except in the first hour in the patients who were given oral Gabapentin 600mg 2 hours before surgery. The total amount of Fentanyl consumed were also significantly less in gabapentin group.

Surgical tissue injury results in neuroplastic changes such as metabolic activation and hyperexcitability of spinal nociceptive neurons which result in development of pathological pain characterized by hyperalgesia and allodynia. Gabapentin decreases postoperative pain by its action of inhibiting the neuroplastic changes associated with acute tissue injury.[3-11]

Gabapentin was also shown in some studies to enhance the analgesic effect of opioids eg. Eckhardt K et al[14]

The dose of 600 mg was selected based on the study by Pandey CK, Navkar DV[11],et al who evaluated the optimal preemptive dose of gabapentin for postoperative pain relief after single-level lumbar diskectomy and its effect on fentanyl consumption during

the initial 24 hours. They concluded that gabapentin 600 mg is the optimal dose for postoperative pain relief.

The pre-emptive administration of gabapentin two hours before surgery appears rational so as to attain the peak plasma concentration at the time of incision.

Many studies have explored the use of Gabapentin as a pre emptive analgesic with mixed results. Most of the studies showed decreased pain scores and opioid-sparing effect during the first 24 h after a single dose of gabapentin 300-1200 mg, administered 1-2 h preoperatively. The opioid sparing effect ranged from 20% to 62%.But there was difference between studies with respect to the incidence of side effects.

Alparslan Turan, MD*, Beyhan Karamanl[21] did a randomized, placebo-controlled, double-blind study,on the efficacy and safety of gabapentin on pain after abdominal hysterectomy and on tramadol consumption.

Similar studies on patients undergoing hysterectomies were also done Dierking by G, Duedahl TH et al and Gilron I, Orr E et al.

In Alparslan Turan study The VAS scores in the sitting and supine position at 1, 4, 8, 12, 16, and 20 h were significantly lower in

the gabapentin group when compared with the placebo group up to 20 h after surgery. The tramadol consumption at 12, 16, 20, and 24 h and total tramadol consumption were significantly less in the gabapentin group when compared with placebo group. Sedation scores were similar at all the measured times. There were no differences between groups in adverse effects.

Dierking by G, Duedahl TH et al observed a significant inverse association between plasma levels of gabapentin at 2 h postoperatively, and morphine usage from 0 to 2 h, and from 0 to 4 h postoperatively. No significant differences in pain at rest or during mobilization, or in side-effects, were observed between groups.

Gilron I, Orr E et al also found significantly reduced pain scores and opioid sparing effect with gabapentin. Adverse effects were similar in all groups except sedation which was more frequent with gabapentin.

The results of these were similar in terms of the pain scores and decreased analgesic requirements to our study. In the former two studies side effects were similar in both placebo and gabapentin group. Gilron I, Orr E et al found sedation to be more frequent in gabapentin

group. in our study sedation and vertigo were significantly higher in patients given gabapentin.

Turan A, Memis D,[24] investigated the efficacy and safety of gabapentin in patients who underwent rhinoplasty or endoscopic sinus surgery patients under monitored anesthesia care. . Postoperative pain scores and intraoperative pain scores at 45 and 60 min were significantly lower in the gabapentin group. Fentanyl (122 ± 40 μg versus 148 ± 42 μg; $P < 0.05$)) consumption was smaller and the time to first analgesic request (18 ± 9 h versus 9 ± 7 h; $P < 0.001$) was longer in the gabapentin group. A more frequent incidence of dizziness was found in the gabapentin (versus placebo) group (24% versus 4%, respectively).The findings are similar to our study including a higher incidence of dizziness (54%)

Turan A, Karamanlioğlu B,et al also extended their study to patients undergoing spine surgeries. they found out that overall, pain scores were significantly lower in the gabapentin group when compared with the placebo group. Total morphine consumption in the gabapentin group was 16.3 +/- 8.9 mg (mean +/- SD) versus 42.8 +/- 10.9 mg in the placebo patients. The incidence of vomiting and urinary retention was significantly ($P < 0.05$) higher in the placebo group, but there was no difference in incidence of other adverse effects between the groups. The findings are similar to our study except that there was no statistically significant difference in incidence of vomiting in our study.34.43% in

gabapentin and 54.545 in placebo(p=0.08).None of our patients also had urinary retention.

. [28]Dirks J, Fredensborg BB did similar study in patients undergoing mastectomies.Gabapentin reduced total morphine consumption from a median of 29 (interquartile range, 21-33) to 15 (10-19) mg (P< 0.0001). Pain during movement was reduced from 41 (31-59) to 22 (10-38) mm at 2 h postoperatively (P < 0.0001) and from 31 (12-40) to 9 (3-34) mm at 4 h postoperatively (P = 0.018). No significant differences between groups were observed with regard to pain at rest or side effects.Al-Mujadi H, A-Refai [19]AR studied gabapentin in thyroidectomies.Overall, pain scores at rest and during swallowing in the gabapentin group were significantly lower when compared with the placebo group. Total postoperative morphine consumption in the gabapentin group was 15.2 +/- 7.6 mg (mean +/- SD) vs 29.5 +/- 9.9 mg in the placebo group (P < 0.001). No significant differences in side effects were observed between groups.

In our study the VAS scores measured at 1st hour after surgery were higher in gabapentin group compared to the placebo but the difference was not statistically significant. This higher VAS scores in the first hour compared to other times in the placebo group could be attributed to the residual analgesic effect of fentanyl given intra

operatively and also to the residual effect of anesthetic which could have influenced the measurement of VAS scoring in both groups. Fassoulaki A, Stamatakis E studied the effect of perioperative gabapentin administration on pain following abdominal hysterectomies. They conclude that Gabapentin attenuates late but not acute pain after abdominal hysterectomy.

Two systematic reviews by Mathiesen O, Møiniche S, Dahl JB and Tiippana EM, Hamunen K, Kontinen VK, showed a significant reduction in morphine. Tiippana EM, Hamunen K, Kontinen VK**,** also said that The most common adverse effects of the gabapentin were sedation and dizziness[32,33]

Despite differences in surgical techniques most of the studies showed significant effect of gabapentin on post operative analgesic requirements. Our results are consistent with these studies.Although there was a higher incidence of sedation and dizziness in gabapentin group, it was well tolerated by the patients and none of them required treatment.Patients are understandably anxious during the perioperative period and this can be a significant problem in some. The higher incidence of sedation with gabapentin in our study could be an added advantage of Gabapentin. Its anxiolytic properties are described by studies by Chouinard G et al and de-Paris F, Sant'Anna MK, et al .[29 30]

SUMMARY

Surgical tissue injury is known to produce neuroplastic changes leading to spinal sensitization and the expression of stimulus-evoked hyperalgesia and allodynia. Anticonvulsants, which were long being used to treat neuropathic pain is found to inhibit these neuroplastic changes from occurring. Among them recent studies have focused the role of gabapentin in post operative pain relief.

This is a prospective, randomized, placebo controlled study to find out if preemptive administration of 600mg oral gabapentin 2 hours before thyroid surgery reduces pain and analgesic requirement in the post operative period.

Data from 35 patients in gabapentin group and 33 patients in placebo group were analyzed. The results showed significantly lower pain scores and analgesic requirements in gabapentin group. There was high incidence of dizziness and higher sedation in patients who had gabapentin.

CONCLUSION

Our study demonstrated that a 600 mg single pre-emptive oral dose of Gabapentin significantly reduces post operative pain and analgesic requirement following thyroid surgeries. There was an increased incidence of sedation and vertigo in patients given gabapentin, but these were well tolerated by the patients. Thus Gabapentin can be considered as an useful adjunctive to opiods in the treatment of post-operative pain.

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